

Pub. No. US 2006/0040894 A1, Hunter, et al.

HA and Lidocaine in the Prior Art

US 2006/0040894 A1

21

Feb. 23, 2006

boxymethyl cellulose all at 10 mg/ml. In order to attain this concentration a dose of approximately 10 times that required dose per ml may be needed (e.g., a total weight of 10 mg indomethacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area or volume that may be exposed to a few ml of aqueous body fluid. So, for example, if 1 ml of an HA solution was injected where the injection fluid may be exposed to perhaps 2 ml of interstitial fluid diffusing past the area then a dose of 100 mg of each of these inhibitors would be recommended to ensure attainment of a dose of 10 mg per ml for some time after. The dosing needs depend largely of the injection volume and the site of application. At sites with a higher hyaluronidase inhibitor may be given in a controlled manner dosage form then the application calculated by one skilled in the art based on the profiles, site of application, turn over rate of the HA in the area and other parameters such as

[0177] 4. HI-Loaded Hyaluronidase Inhibitor

[0178] A variety of injectable hyaluronidase inhibitors have been developed for soft tissue augmentation and to correct facial scars, diminish facial lines. Specifically, such implants are indicated for a variety of contour deficiencies including correction of acne scars, atrophy, glabellar frown lines, nasolabial folds, rhinoplasty, skin graft or other tissue defects. Manufactured synthetically and commercially available for this purpose are HYLAFORM (B) from Genzyme Corporation. Other commercial HA products that may be combined with HA in cosmetic injections include: ACI HA (Kaisha, Ltd. (Japan)), JUVEDERM from L.E.A. (France), MACDERMOL from Laboratoires O.R. GE V. (France), MACDERMOL from Laboratoires O.R. GE V. (France), and ROFILAN Hyal Gel from Rofil Medical International (Holland).

[0179] Unfortunately, repeated "touch up" procedures are often required as the implant is colonized by host connective tissue cells and inflammatory cells which produce hyaluronidase and other enzymes capable of breaking down the HA implant over time. An injectable hyaluronic acid containing a hyaluronidase inhibitor (HI), both alone or in a sustained release preparation, can result in increased durability of the implant and reduce the number of subsequent repeat injections. Although any of the previously described hyaluronidase inhibitors may be suitable for incorporation into a dermal HA injection, the following are particularly preferred: aurothiomalate, indomethacin, propylene glycol, dextran sulphate, fucoidan, heparin, flavonoids, agents that modulate allergic reactions, phenolic compounds, and carboxymethyl cellulose.

[0180] Regardless of the formulation utilized, administration of the HI-loaded HA injection may proceed in the following manner. A pre-loaded syringe with a fine gauge needle (30 or 32 gauge) containing the HI-HA implant material is used. The patient is placed in a sitting position with the table back slightly reclined. Topical lidocaine and/or prilocalne can be used for anesthesia. The needle is inserted at an angle to the skin and advanced into the

superficial dermal tissue. A sufficient amount of implant material is extruded to repair the soft tissue contour defect. In the case of HI-loaded RESTYLANE, overcorrection (injection of more material than is ultimately needed) is required as some of the injected material dissipates in the hours following injection. HI-loaded PERLANE is typically used to correct deeper lines and is injected deeper into the dermis.

[0181] Representative examples of hyaluronic acid compositions used in cosmetic surgery injections are described in U.S. Pat. Nos. 5,633,001; 5,256,140, and 6,703,041.

[0183] The HA-HI composition may further comprise an anesthetic such as lidocaine, benzocaine or prilocalne and/or a neurotoxin such as a botulinum toxin.

REPEL or FLOWGEL, and other low molecular weight polymers that can be excreted.

[0183] The HA-HI composition may further comprise an anesthetic such as lidocaine, benzocaine or prilocalne and/or a neurotoxin such as a botulinum toxin.

[0184] It should be apparent to one of skill in the art that potentially any hyaluronidase inhibitor may be utilized alone, or in combination, in the practice of this embodiment as described above. Exemplary HI agents for use in combination with HA in cosmetic injection procedures include aurothiomalate, indomethacin, propylene glycol, carboxymethyl cellulose, dextran sulphate, fucoidan and heparin, as well as analogues and derivatives of the aforementioned.

[0185] Suitable doses of these compounds may be such as to provide a steady concentration of each agent to elicit a prolonged inhibitory effect on hyaluronidase. These concentrations are approximate and may be adjusted depending on the potency of the compound and duration of effect required: aurothiomalate 10 mM, indomethacin 1 mg/ml, heparin 1 mg/ml, sulphated polysaccharides 2 mg/ml, and propylene glycol, TRITON X-100, PEG, SPAN, PLURONIC L101, and carboxymethyl cellulose all at 10 mg/ml. In order to attain this concentration a dose of approximately 10 times that required dose per ml may be needed (e.g., a total weight of 10 mg indomethacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area that may be

Lidocaine in the Prior Art

Crosslinked HA Fillers with Lidocaine Were Already Used

PURAC



Patents In Dispute

US Patent No. 8,450,475 B2



US008450475B2

(12) **United States Patent**
Lebreton

(10) **Patent No.:** **US 8,450,475 B2**
(45) **Date of Patent:** **May 28, 2013**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

(75) **Inventor:** **Pierre F. Lebreton, Annecy (FR)**

(73) **Assignee:** **Allergan, Inc., Irvine, CA (US)**

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 656 days.

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(22) **Filed:** **Feb. 26, 2009**

(65) **Prior Publication Data**
US 2010/0028437 A1 Feb. 4, 2010

Related U.S. Application Data

(60) Provisional application No. 61/085,956, filed on Aug. 4, 2008, provisional application No. 61/087,934, filed on Aug. 11, 2008, provisional application No. 61/096,278, filed on Sep. 11, 2008.

(51) **Int. Cl.**
C07H 1/00 (2006.01)

(52) **U.S. Cl.**
USPC **536/124; 514/54; 424/484; 424/488**

(58) **Field of Classification Search**
USPC **536/124; 514/54; 424/484, 488**
See application file for complete search history.

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ABSTRACT

Disclosed herein are soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acids and pharmaceutically acceptable salts thereof. In one aspect, hyaluronic acid-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent, for example, lidocaine. The present hyaluronic acid-based compositions including lidocaine have an enhanced stability, relative to conventional compositions including lidocaine, for example when subjected to sterilization techniques or when stored for long periods of time. Methods and processes of preparing such hyaluronic acid-based compositions are also provided.

37 Claims, 1 Drawing Sheet

US Patent No. 8,357,795 B2



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(12) **United States Patent**
Lebreton

(10) **Patent No.:** **US 8,357,795 B2**
(45) **Date of Patent:** ***Jan. 22, 2013**

(54) **HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE**

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(73) **Assignee:** **Allergan, Inc., Irvine, CA (US)**

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(51) **Int. Cl.**
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USPC **536/124; 514/54; 424/488**

(58) **Field of Classification Search**
USPC **536/124; 514/54; 424/484, 488**
See application file for complete search history.

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ABSTRACT

Disclosed herein are cohesive soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acids and pharmaceutically acceptable salts thereof. In one aspect, hyaluronic acid-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent, for example, lidocaine. The present hyaluronic acid-based compositions including lidocaine have an enhanced stability and cohesivity, relative to conventional compositions including lidocaine, for example when subjected to sterilization techniques or when stored for long periods of time. Methods and processes of preparing such hyaluronic acid-based compositions are also provided.

41 Claims, 5 Drawing Sheets

Law of Claim Construction

Claim construction favors the meaning that “most naturally aligns with the patent's description of the invention.”

Phillips v. AWH Corp., 415 F.3d 1316 (Fed. Cir. 2005)(en banc)

"[T]he focus in claim construction is on 'the meaning of claim terms within the patent,' and not on the abstract meaning of words."

Reflex Packaging Inc. v. Lenovo (United States), Inc., No. 5:10-CV-01002-EJD, 2012 U.S. Dist. LEXIS 64594, at *20 (N.D. Cal. May 8, 2012)

First Disputed Term: “Stable”

Claim Term (Claim)	Plaintiffs’ Construction	Defendants’ Construction
Stable (1, 18, 27, 31, 34)	Resists chemical and physical decomposition	Maintains one of the following aspects: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

3

In still another embodiment, the soft tissue filler composition has an extrusion force of between about 10 N and about 13 N, for example, at a rate of about 12.5 mm/minute. In yet another embodiment, the composition has a viscosity of between about 5 Pa*s and about 450 Pa*s, for example, when measured at about 5 Hz.

In one embodiment, the HA component is a gel, for example, a cohesive, hydrated gel. In one embodiment, the HA component is a crosslinked HA gel having no greater than about 1% to about 10% free HA. For purposes of this disclosure, free HA includes truly uncrosslinked HA as well as lightly crosslinked HA chains and fragments, all in soluble form in water.

In yet other embodiments, the HA component comprises greater than about 10%, for example, greater than about 15%, for example, up to or greater than about 20% free HA.

In yet another embodiment, the HA component is a gel comprising particles of crosslinked HA in a relatively fluidic medium of free HA. In some embodiments, the HA component has an average particle size of greater than about 200 µm, for example, greater than about 250 µm.

Further described herein is a soft tissue filler composition comprising: a HA component crosslinked with 1,4-butanediol diglycidyl ether (BDDE), said HA component having a degree of crosslinking of less than about 5%, for example, about 2%, and an anesthetic component having a concentration between about 0.1% and about 5.0% by weight of the soft tissue filler composition, wherein the anesthetic is lidocaine.

Further described herein are methods of preparing soft tissue filler compositions, the methods comprising the steps of: providing a HA component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyl ether, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, and 1,4-butanediol diglycidyl ether or combinations thereof; adjusting the pH of said HA component to an adjusted pH above about 7.2; and adding a solution containing at least one anesthetic agent to the HA component having the adjusted pH to obtain a HA-based filler composition.

In another embodiment, the composition is sterilized, for example, by autoclaving, to form a sterilized composition and wherein the sterilized composition is stable at ambient temperature for at least about 6 months, for example, at least 9 months, at least about 12 months or more.

In still another embodiment, the adjusted pH is above about 7.5. In another embodiment, the method further comprises the step of homogenizing the HA component during or after the step of adding the solution containing the at least one anesthetic agent. In a further embodiment, the step of homogenizing comprises subjecting the composition to mixing with a controlled shear.

In another embodiment, the step of providing a HA component comprises providing dry free NaHA material and hydrating the dry free NaHA material in an alkaline solution to obtain an alkaline, free NaHA gel. In yet another embodiment, the alkaline, free NaHA gel has a pH greater than about 8.0. In still another embodiment the pH is greater than about 10.

In a further embodiment, the HA component comprises greater than about 20% free HA and the crosslinked portion of the HA component has a degree of crosslinking of less than about 6% or less than about 5%.

In still a further embodiment, the soft tissue filler composition has a particulate nature in that it comprises particles of crosslinked HA dispersed in a fluid soluble HA medium. In

4

some embodiments, the average size of such particles is at least about 200 µm, and in other embodiments the average size of such particles is at least about 250 µm.

DEFINITIONS

Certain terms as used in the specification are intended to refer to the following definitions, as detailed below. Where the definition of terms departs from the commonly used meaning of the term, applicant intends to utilize the definitions provided below, unless specifically indicated.

Autoclave stable or stable to autoclaving as used herein describes a product or composition that is resistant to degradation such that the product or composition maintains at least one, and preferably all, of the following aspects after effective autoclave sterilization: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration.

Patentee Can Be His Own Lexicographer

Where the "patent expresses an intention to impart a novel meaning to claim terms,"¹ that definition "controls the meaning of [the claim term], regardless of any potential conflict with the term's ordinary meaning"² Thus, a claim term should not be given its "plain and ordinary meaning" where "the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term"³ These changes to a term's definition can be found not only in the patent itself, but also the prosecution history, which can "provide[] evidence of how the PTO and the inventor understood the patent."⁴

¹*SunRace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1302 (Fed. Cir. 2003).

²*3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1374 (Fed. Cir. 2003).

³*SunRace*, 336 F.3d at 1304.

⁴*Phillips*, 415 F.3d at 1317; *Vitronics*, 90 F.3d at 1582-83.

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

5 ing agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of HA monomers to crosslinker (HA monomers: crosslinker).

Free HA as used herein refers to individual HA polymer molecules that are not crosslinked to, or very lightly crosslinked to (very low degree of crosslinking) the highly crosslinked (higher degree of crosslinking) macromolecular structure making up the soft tissue filler composition. Free HA generally remains water soluble. Free HA can alternatively be defined as the "uncrosslinked," or lightly crosslinked component of the macromolecular structure making up the soft tissue filler composition disclosed herein.

Cohesive as used herein is the ability of a HA-based composition to retain its shape and resist deformation. Cohesiveness is affected by, among other factors, the ratio of the initial free HA, the amount of residual free HA following based composition pH. A cohesive resists phase separation when tested as disclosed in Example 1 herein.

DETAILED DESCRIPTION

The present disclosure generally describes, for example, dermal and subcutaneous hyaluronic acids (HA) and pharmaceutical compositions of HA, for example, sodium hyaluronate. HA-based compositions of therapeutically effective amount, for example, lidocaine. The compositions including at least one anesthetic agent, for example, lidocaine, to enhance stability, relative to compositions including, for example, to high temperatures and pressure, experienced during heat and/or pressure, for example, autoclaving, and/or ambient temperature for an extended period of time.

The stable compositions maintain the following aspects after effective and/or prolonged storage: transparent appearance, extrusion force and consistency, HA concentration, sterility, concentration. Methods or processes based compositions are also produced by such methods or processes.

As used herein, hyaluronic acid, hyaluronate salts, and includes, but not limited to, sodium hyaluronate (NaHA), potassium hyaluronate, calcium hyaluronate.

Generally, the concentration of HA in the compositions described herein is preferably at least 10 mg/mL and up to about 40 mg/mL. For example, the concentration of HA in some of the compositions is in a range between about 20 mg/mL and about 30 mg/mL. Further, for example, in some embodiments, the compositions have a HA concentration of about 22 mg/mL, about 24 mg/mL, about 26 mg/mL, or about 28 mg/mL.

In addition, the concentration of one or more anesthetics is in an amount effective to mitigate pain experienced upon injection of the composition. The at least one local anesthetic can be selected from the group of ambucaine, amolanone, amylocaine, benoxinate, benzocaine, bexocaine, biphenamine, bupivacaine, butacaine, butamben, butanilcaine, butethamine, butoxyacaine, carticaine, chlorprocaine, cocaine, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, dipreron, dicyclomine, egonidine,

6 egonine, ethyl chloride, etidocaine, beta-eneine, euprocin, fenacamine, fomocaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucinecaine mesylate, levonadol, lidocaine, mepivacaine, meprycaine, metabutoxycaine, methyl chloride, myrtacaine, neopaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, and salts thereof. In one embodiment, the at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl. The compositions described herein may have a lidocaine concentration of between about 0.1% and about 5% by weight.

The stable compositions maintain at least one of, or all of, the following aspects after effective autoclave sterilization and/or prolonged storage: transparent appearance, pH for use in a patient, extrusion force and/or rheological characteristics, HA concentration, sterility, osmolarity, and lidocaine concentration.

appearance and other characteristics, for example, stored for a lengthy period of time, for example, for a period of time of at least 6 months to a year or more, and even after being subjected to sterilization procedures, for example, autoclaving.

It is a surprising discovery that formulations of crosslinked HA-based compositions including lidocaine can be manufactured in a manner in accordance with the invention to produce sterilization-stable, injectable HA/lidocaine compositions.

Further described herein is a method for preparing stable HA-based compositions containing an effective amount of lidocaine by preparing a cohesive, crosslinked HA-based precursor composition, adding lidocaine hydrochloride to the precursor composition to form a HA/lidocaine gel mixture, and homogenizing the mixture, to obtain a crosslinked HA-based composition that is stable to autoclaving.

In certain embodiments, the precursor composition is a gel which includes less than about 1% of soluble-liquid form or

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

13

between about 7.5 and about 8). The lidocaine HCl solution is then added to the slightly basic gel to reach a final desired concentration, for example, a concentration of about 0.3% (w/w). The resulting pH of the HA/lidocaine mixture is then about 7 and the HA concentration is about 24 mg/ml.

Mechanical mixing is performed in order to obtain a proper homogeneity in a standard reactor equipped with an appropriate blender mechanism.

If desired, a suitable amount of free HA gel may be added to the HA/lidocaine gel mixture with the advantage of increasing the kinetics of lidocaine delivery. For example, free HA fibers are swollen in a phosphate buffer solution, in order to obtain a homogeneous viscoelastic gel. This free HA gel is then added to the crosslinked HA/lidocaine gel (for example, at about 5% w/w). The resulting gel is then filled into Ready-to-Fill sterile syringes and autoclaved at sufficient temperatures and pressures for sterilization for at least about 1 minutes.

After autoclaving, the final HA/lidocaine product is packaged and distributed to physicians. The product manufactured in accordance with this method exhibits one or more characteristics of stability as defined elsewhere herein. For example, the autoclaved HA/lidocaine product has a viscosity, cohesivity, and extrusion force that are acceptable. No degradation of the HA/lidocaine gel product is found during testing of the product after the product has spent several months in storage.

Example 3

Properties of Soft Tissue Fillers

Properties of HA/lidocaine compositions manufactured in accordance with methods described herein are shown in the Table 1 below. Extrusion force for example was measured using an INSTRON® Advanced Materials Testing System Model 5564 (Instron, Norwood, Mass.) running BLUE-HILL® software version 2.11 (Instron, Norwood, Mass.).

TABLE 1

HA/lidocaine Composition	
Appearance	Homogeneous transparent gel
pH	7.2
Extrusion Force (N)	10.8N
NaHA Content	23.7 mg/g
Sterility	Sterile (SAL $\leq 10^{-6}$)
Osmolality	321 mOsm/kg
Lidocaine Content (%)	0.29%
2,6-dimethylaniline content	Conforms

In order to ensure that product specifications were maintained throughout the shelf life of the composition, multiple studies were performed. In addition, 2,6 dimethylaniline content was measured in order to confirm the absence of lidocaine degradation.

14

Table 2 provides a summary of stability testing results on the composition manufactured as described herein.

TABLE 2

Test	3 month results	6 month results	9 month results
Aspect Transparent and homogeneous	Conforms	Conforms	Conforms
pH	7.2	7.2	7.2
Extrusion Force (N)	11.9	11.1	11.9
NaHA Concentration (mg/g)	23.8	23.1	24.2
Sterility	Conforms	Conforms	Conforms
Osmolality (mOsm/kg)	349	329	342
Lidocaine Content (%)	0.29	0.29	0.29
2,6-dimethylaniline content	Conforms	Conforms	Conforms

It was discovered that at 9 months time (from manufacture date), the composition continues to meet the product specifications.

Example 4

Kinetic Release

The following example illustrates the kinetic of release of lidocaine from cohesive HA gels according to the present description. The aim of the Example is to show that the lidocaine contained in HA gels according to the present description is freely released from the gels when placed in the skin.

Dialysis was performed for different periods of time (about 10 g of gel were placed in a small dialysis bag and then put in 30 g of water). After each dialysis was stopped at a given time, the gel was homogenized with a spatula and the amount of lidocaine was determined by UV method. The final concentration of the dialysis bath met the theoretical concentration of lidocaine which indicates the free release of lidocaine from the gel.

Table 3 illustrates lidocaine concentration in % (w/w), correction of the value and determination of the % of released lidocaine. Additionally, FIG. 1 graphically illustrates the results tabulated in Table 3 below. Within FIG. 1 is indicated the theoretical equilibrium concentration of lidocaine that would exist if the lidocaine were retained in the gel or if it were to be freely released. As is graphically illustrated therein, the data suggest that the lidocaine is freely released from the gel.

TABLE 3

	MMA4031-	MMA4031-	MMA4031-	MMA4031-	MMA4031-	MMA4031-	MMA4031-
	EC6	EC2	EC3	EC4	EC5	EC7	EC7
Dialysis time (hr)	0 hr	1 hr 30 min	5 hr	7 hr	23 hr	48 hr	72 hr
[lidocaine] (%)	0.29	0.20	0.16	0.15	0.08	0.07	0.07

Table 2 provides a summary of stability testing results on the composition manufactured as described herein.

TABLE 2

Test	3 month results	6 month results	9 month results
Aspect Transparent and homogeneous	Conforms	Conforms	Conforms
pH	7.2	7.2	7.2
Extrusion Force (N)	11.9	11.1	11.9
NaHA Concentration (mg/g)	23.8	23.1	24.2
Sterility	Conforms	Conforms	Conforms
Osmolality (mOsm/kg)	349	329	342
Lidocaine Content (%)	0.29	0.29	0.29
2,6-dimethylaniline content	Conforms	Conforms	Conforms

It was discovered that at 9 months time (from manufacture date), the composition continues to meet the product specifications.

Second Disputed Term: “Crosslinked” ‘475 Patent

Claim Term (Claim)	Plaintiffs’ Construction	Defendants’ Construction
HA crosslinked with 1,4-butanediol diglycidyl ether (BDDE) / hyaluronic acid (HA) component crosslinked with 1,4-butanediol diglycidyl ether (BDDE) / (BDDE)-crosslinked hyaluronic acid (1, 18, 27, 31, 34)	HA that forms a macromolecular structure resulting from chemical linking of HA by BDDE	HA that has been covalently modified with BDDE to form a macromolecular structure that is water-insoluble , such that the degree of crosslinking is at least about 2% and is up to about 20% “Degree of crosslinking” as used herein has the same construction as agreed by the parties

Second Disputed Term: “Crosslinked” ‘795 Patent

Claim Term (Claim)	Plaintiffs’ Construction	Defendants’ Construction
Hyaluronic acid (HA) component crosslinked with a crosslinking agent (1)	HA that forms a macromolecular structure resulting from chemical linking of HA by a crosslinking agent	<p>HA that has been covalently modified with a crosslinking agent to form a macromolecular structure that is water-insoluble, such that the degree of crosslinking is at least about 2% and is up to about 20%</p> <p>“Degree of crosslinking” as used herein has the same construction as agreed by the parties within the ‘475 Patent</p>

Agreed-Upon Constructions

'475 Patent

Claim Term (Claim)	Agreed-Upon Construction
Degree of crosslinking (5-7, 18, 27, 31, 37)	<p>The percent weight ratio of crosslinking agent to HA monomeric units (HA disaccharide units) within the crosslinked portion of the HA based composition (i.e., (total mass of crosslinking agent / total mass of monomeric units) * 100))</p> <p>The “crosslinked portion of the HA based composition” as used herein has the same construction as the other terms referring to “crosslinked HA,” as construed by the court</p>

Second Disputed Term: “Crosslinked”

- **Covalently modified**
- **Water-insoluble**
- **Degree of crosslinking**

Second Disputed Term: “Crosslinked”

- **Covalently modified**
- Water-insoluble
- Degree of crosslinking

7,902,171 B2 Patent, Reinmuller

Art Describes Crosslinks as Covalent Bonds

US 7,902,171 B2

1 COMPOSITION FOR TREATING INFLAMMATORY DISEASES

The present invention relates to the use of hyaluronic acid for treating inflammatory diseases, in particular skin diseases or mucous membrane diseases.

A great number of skin diseases, in particular those of the atopic type, have not been explained causally. Commonly, these diseases are inflammatory reactions of the dermis and of the dermoepithelial transition zone. It is known that in these diseases, considerable shifts in the normal hyaluronic acid content in the dermis and epidermis occur. The treatment of such diseases at present consists in various measures, e.g. administration of fat-containing ointments, creams or lotions with addition of different active compounds. Most effectively, such inflammatory diseases, however, are treated with corticoid-containing preparations for external (topical) use. The adequately known local and systemic side effects of the corticoids (derivatives of the endogenous steroid hormone cortisol) are to be expected here. In the case of chronic use of the topical corticoid preparations, as a rule delayed consequences occur, such as, for example, cutaneous atrophy.

Another means of treatment consists in the use of agents which attack cells of the immune system and inhibit the biosynthesis of immunomodulators, such as, for example, cyclosporin, tacrolimus and pimecrolimus. Substances having such actions are also described as immunosuppressants, because they suppress the immune response of a biorganism. Their use is thus considerably restricted, since an intact immune system is essential for a permanently satisfactory state of health. Use is thus suitable only in the case of severe symptoms and in physically mature individuals. Long-term risks and the risks of long-term use, such as, for example, carcinogenicity, are completely unexplained.

There is therefore a need to develop new agents for treating inflammatory skin diseases or mucous membrane diseases, in which the disadvantages of the prior art can be at least partly avoided.

Surprisingly, it has been found that hyaluronic acid, a glycosaminoglycan, is outstandingly suitable for treating inflammatory skin diseases or mucous membrane diseases, in particular of inflammatory skin diseases of the atopic type.

One subject of the invention is thus the use of hyaluronic acid for the production of a composition for preventing or treating inflammatory skin diseases or mucous membrane diseases.

A further subject of the invention is a process for preventing or treating an inflammatory skin or mucous membrane disease, where a preparation is administered to a subject to be treated, for example a human patient or alternatively an animal, which contains hyaluronic acid in an amount adequate for treating the disease.

The administration of hyaluronic acid can in principle be carried out in any desired manner, provided this is suitable for treating the respective disease. In many cases, local administration is carried out in the area of the diseased skin site, e.g. a lesion. Preferably, administration is carried out intradermally, e.g. by injection, or by topical application to the diseased skin site.

For the treatment of inflammatory skin diseases, hyaluronic acid is suitable both in uncrosslinked form and in crosslinked form or mixtures thereof. Uncrosslinked hyaluronic acid is preferably selected from (i) long-chain hyaluronic acid having an average molecular weight (weight-average) of at least 200 kD and (ii) short-chain hyaluronic acid having an average molecular weight (weight-average) up to 50 kD or mixtures thereof.

2

Crosslinked hyaluronic acid can be, for example, covalently or noncovalently crosslinked. The preparation of crosslinked hyaluronic acid can be carried out per se in a known manner. Covalent crosslinkage can in general be carried out here by crosslinking with bifunctional reactive agents, such as, for example, glutaraldehyde or carbodiimide, via bifunctional amino acids, e.g. lysine, prolamines or albumins. It is also possible, however, to produce crosslinkages by means of an amide, ester or ether bond for example. Further suitable reagents for the covalent crosslinkage of hyaluronic acid are ethylene glycol diglycidyl ether or 1,4-butanediol diglycidyl ether, divinyl sulfone, photocrosslinking reagents, such as ethyleosin, hydrazides, such as bishydrazide, trishydrazide and polyvalent hydrazide compounds. Furthermore, intra- or/and intermolecularly esterified hyaluronic acid derivatives can also be employed.

using multivalent metal ions, such as, for example, iron, copper, zinc, calcium, magnesium, barium and other chelating metal ions is particularly preferred.

Hyaluronic acid crosslinked state (e.g. acid from Biomatrix, Pat. No. 4,713,448).

In use, the molecular weight of the hyaluronic acid is not particularly important, which, however, is preferably 10% or more, without being observed that with lower molecular weights crosslinking suffices.

The hyaluronic acid can be employed by itself, for example, in the form of a gel or as a solution.

The pharmaceutical composition according to the invention contains the hyaluronic acid in an amount of 0.01 to 20% by weight, in particular 0.1 to 1% by weight.

As pharmaceutical compositions according to the invention, agents for pH adjustment, solubilizers, penetration enhancers or/and gel-forming agents in such preparations are also suitable.

In addition to the hyaluronic acid, the pharmaceutical composition can optionally also contain other active compounds which, in the course of application to skin diseases (dermatitis, eczema, psoriasis, etc.), can be beneficial.

Such active compounds are, for example, antibiotics (e.g. penicillin, tetracycline, erythromycin, etc.), antifungals (e.g. clotrimazole, etc.), corticosteroids (e.g. hydrocortisone, etc.), vitamins (e.g. vitamin A, vitamin E, etc.), skin care agents and/or circulation-promoting (hyperem-

means of an amide, ester or ether bond for example. Further suitable reagents for the covalent crosslinkage of hyaluronic acid are ethylene glycol diglycidyl ether or 1,4-butanediol diglycidyl ether, divinyl sulfone, photocrosslinking reagents, such as ethyleosin, hydrazides, such as bishydrazide, trishydrazide and polyvalent hydrazide compounds. Furthermore, intra- or/and intermolecularly esterified hyaluronic acid derivatives can also be employed. A noncovalent crosslinkage using multivalent metal ions, such as, for example, iron, copper, zinc, calcium, magnesium, barium and other chelating metal ions is particularly preferred.